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EXAMINER

STEADMAN, DAVID J

ART UNIT PAPER NUMBER

1652

DATE MAILED: 11/05/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/051,013

Applicant(s)

BESTOR, TIMOTHY H.

Examiner

David J. Steadman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 August 2002.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-26, 29 and 34-47 is/are pending in the application.
- 4a) Of the above claim(s) 15-17, 19-23, 34-41 and 47 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-14, 18, 24-26, 29, and 42-46 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

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DETAILED ACTION

Application Status

Claims 1-26, 29, and 34-47 are pending in the application.

Applicants' election with traverse of Group I, claims 1-4, 6-26, 29, and 42-46 and the species of Group H, drawn to a gene associated with an infectious disease in Paper No. 18, filed 08/27/02, is acknowledged.

Election/Restrictions

1. Applicants traverse the restriction requirement on the grounds that the inventions of Groups I-IV as set forth in the restriction requirement of Paper No. 17 are neither independent nor distinct and a search for the inventions of Groups I-IV would not be a serious burden on the examiner. Applicants argue that the examiner consider claim 1 a linking claim and that at least Groups I and II should be rejoined. Applicants' argument is not found persuasive. It is noted that the inventions listed as Groups I-IV were not restricted under only 35 USC 121 as the instant case was filed under 35 USC 371. The inventions were instead found to lack unity of invention under 35 USC 121 and 372 because said inventions lack the same or corresponding technical feature for the reasons previously described (see particularly paragraph 2 of Paper No. 17). As a lack of unity was made, the examiner need not meet the criteria for restriction defined for US practice. Furthermore, because the inventions do not share a special technical feature for the reasons set forth in paragraph 2 of Paper No. 17, lack of unity is appropriate. Regarding applicants' request for rejoinder of Groups I and II, it is noted that the inventions of Groups I and II may not be patentably distinct and therefore, the examiner has elected to rejoin Groups I and II.

Claims 15-17, 19-23, 34-41, and 47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention (claims 34-41 and 47) or species (claims 15-17 and 19-23), there being no allowable generic or linking claim.

The requirement is still deemed proper and is therefore made FINAL.

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Claims 1-14, 18, 24-26, 29, and 42-46 are being examined to the extent the claims read on the elected subject matter.

Claim Objections

2. Claim 6 is objected to because of the recitation of "*M.SssI*". Abbreviations, unless otherwise obvious, should not be recited in the claims without at least once reciting the entire phrase for which the abbreviation is used, e.g., "Spiroplasma MQ1 DNA methyltransferase (*M.SssI*)". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 1-14, 18, 24-26, 29, and 42-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 1 (claims 2-14, 18, 24-26, 29, and 42-46 dependent therefrom) is indefinite in the recitation of "binds sufficiently close to the gene's promoter sequence to permit methylation of a methylation site within the promoter". It is noted the term "binds sufficiently close" is defined in the specification at page 14. However, based on this definition, one of skill in the art would not necessarily recognize the relative proximity of binding to a gene's promoter that is required for methylation. It is suggested that applicants clarify the meaning of the term.

b. Claims 2, 3, 12, and 13 (claim 14 dependent therefrom) recite the limitation "the target gene". There is insufficient antecedent basis for this limitation in the claim.

c. Claim 9 is indefinite in the recitation of "a pLS vector". It is unclear from the specification as to which elements are required for "a pLS vector". The specification discloses a diagram of "a

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pLS vector" in Figure 6. However, it is unclear as to the characteristics which are to be included in "a pLS vector" that would distinguish this vector from other vectors. It is suggested that applicants clarify the meaning of the claim.

d. Claim 18 is confusing as claim 15 from which claim 18 depends does not recite an "infectious disease" as a claim limitation. There is insufficient antecedent basis for the limitation of "the infectious disease" in claim 18. It is suggested that, for example, applicants insert the limitation of "an infectious disease" in claim 15.

e. Claim 29 is indefinite because the claim depends from cancelled claim 28. It is suggested that applicants clarify the meaning of the claim.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-14, 18, 24-26, 29, and 42-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is drawn to a genus of chimeric proteins for inhibiting the expression of a gene comprising a DNA methyltransferase with attenuated DNA binding activity and a DNA binding protein that binds to a gene's promoter sequence for methylation of the promoter. Claim 2 limits the promoter of claim 1 to a 5' LTR of HIV-1 proviral DNA. Claim 3 further limits the gene of claim 1. Claims 4-6 further limit the chimeric protein of claim 1. Claim 7 is drawn to an expression vector encoding the chimeric protein of claim 1. Claims 8-10 further limit the vector of claim 7. Claim 11 is drawn to a method for inhibiting gene expression by contacting a promoter with a chimeric protein of claim 1 to methylate the

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promoter. Claims 12-14, 18, 24-26, and 29 further limit the gene or contacting step of claim 11. Claim 42 is drawn to a host cell comprising the vector of claim 7 and claim 43 further limits the host cell of claim 42. Claim 44 is drawn to a pharmaceutical composition comprising the vector of claim 7. Claims 45 and 46 further limit the pharmaceutical composition of claim 44. The claims are rejected because the genus of claimed chimeric proteins has not been fully described in the specification. Specifically, the specification does not disclose the structure of a species of the claimed genus of chimeric proteins. The specification fails to describe any representative species by any identifying characteristics or properties other than the functionality of: being a chimeric protein with the recited functional characteristics (claims 1-6) or a method of use thereof (claims 11-14, 18, 24-26 and 29), being a nucleic acid encoding a chimeric protein (claims 7-10), being a host cell comprising a vector encoding a chimeric protein (claims 42 and 43), or being a pharmaceutical composition comprising a vector encoding a chimeric protein (claims 44-46). The CAFC in *UC California v. Eli Lilly*, (43 USPQ2d 1398) stated that: "In claims to genetic material, however a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA", without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus". Similarly with the claimed genus of chimeric proteins, the functional definition of the genus does not provide any structural information commonly possessed by members of the genus that distinguish the protein species within the genus from other proteins such that one can visualize or recognize the identity of the members of the genus. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

5. Claims 1-14, 18, 24-26, 29, and 42-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one

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skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Undue experimentation is required to make and/or use the claimed invention. Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-6 are so broad as to encompass all chimeric proteins comprising any DNA methyltransferase, any CpG-specific DNA methyltransferase, any cytosine methyltransferase, any mutated mammalian DNA methyltransferase, or *Spiroplasma* sp. strain MQ1 (M.SssI) with attenuated DNA binding activity and any DNA binding protein, any zinc three-finger DNA binding protein, and any mutated LexA binding protein that binds to a gene's promoter sequence for methylation of the promoter. Claims 7-10, 42, and 43 are so broad as to encompass any vector that encodes all chimeric proteins of claim 1 or a host cell comprising said vector. Claims 11-14, 18, 24-26 and 29 are so broad as to encompass a method for inhibiting any gene expression or any of the genes of claims 12-25 by contacting a promoter with all chimeric proteins of claim 1 to methylate the promoter and inhibit gene expression. Claims 44-46 are so broad as to encompass a pharmaceutical composition comprising the vectors of claim 7 encoding all chimeric proteins as recited in claim 1. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of chimeric proteins, methods of use thereof, encoding nucleic acids, and target genes broadly encompassed by the claims.

Regarding claims 1-14, 18, 24-26, 29, 42, and 43, the ability to isolate proteins or nucleic acids encoding proteins with altered functionality, in this case attenuated DNA binding activity, is highly unpredictable. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the

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protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. Furthermore, the specification has not provided guidance as to which amino acids or regions of any DNA methyltransferase, any CpG-specific DNA methyltransferase, any cytosine methyltransferase, any mutated mammalian DNA methyltransferase, or *Spiroplasma* sp. strain MQ1 (M.SssI) amino acid sequence may be modified with an expectation of not only generating a protein with attenuated DNA binding, but to also generate a protein which maintains methyltransferase enzymatic activity. The unpredictability of generating such mutants is readily affirmed by applicants as the specification at page 40 discloses, "[i]t cannot be predicted as to which mutations might give the desired reduction in affinity for DNA". While applicants disclose a method of screening for such mutants, the specification discloses (at page 42, lines 4-7) that such screening may not be successful, further corroborating the unpredictability of generating the desired DNA methyltransferase. It is noted that the specification does not disclose specific mutations of a DNA methyltransferase, a CpG-specific DNA methyltransferase, a cytosine methyltransferase, a mutated mammalian DNA methyltransferase, or M.SssI that would enable a skilled artisan to make a methyltransferase with attenuated DNA binding activity. Thus, a skilled artisan would be required to generate the desired methyltransferase without guidance as to which of the possible amino acid substitutions would likely be successful. It is noted that the specification discloses that the DNA binding protein must also be mutated to meet specific criteria as set forth at pages 44 and 45. The claimed chimeric proteins are not so limited to comprising a DNA binding protein fulfilling these criteria and, as discussed above for the methyltransferase, no specific

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mutations have been disclosed that would enable a skilled artisan to make a DNA binding protein with the desired characteristics as set forth in the specification at pages 44 and 45.

The ability of a DNA binding protein bind "sufficiently close" to allow methylation of a methylation site in order to inhibit gene expression is highly dependent upon the selected combination of a specific DNA methyltransferase-DNA binding protein (see page 39, lines 3-10), the linker sequence joining the two proteins (see page 45, lines 30-35), and the site(s) of methylation within a promoter sequence that, upon methylation result in suppression of transcription (see page 44, line 26 to page 45, line 8). A seemingly infinite amount of experimentation is required to identify the combination of DNA methyltransferase-DNA binding protein chimera, the linker sequence joining the two proteins, and the DNA binding protein-targeted promoter sequence/methylation site(s) for successful inhibition of gene expression. The specification provides guidance in the form of only 2 working examples of the claimed chimeric protein – a mutant M.SssI linked via a 9 amino acid linker to a mutant LexA binding protein (see Example 3) for use in inhibiting expression from an HIV 5'-LTR (Examples 5 and 7) and Hepatitis B virus (Example 6). However, there is no disclosure in the specification as to specific mutations in the sequence of M.SssI or LexA that would result in the desired chimeric protein that has the ability to suppress gene expression from any of the genes of claims 12-25.

Regarding claims 44-46, the term "pharmaceutical" implies use as a treatment of a disease. It is unpredictable what diseases can be effectively treated using a "pharmaceutical composition" comprising a vector of claim 7 encoding a chimeric protein of claim 1. Neither the specification nor the prior art provide sufficient guidance as to what specific diseases could be successfully treated by administering a "pharmaceutical composition" comprising said vector, and attempting to identify a disease treatable using such a "pharmaceutical composition" would constitute undue experimentation. While the specification provides in vitro experimental results that suggest that a *specific* chimeric protein inhibits gene expression from a *specific* promoter (see Examples 4-7 beginning at page 47 of the instant specification), the specification provides no indication that the claimed chimeric proteins as broadly claimed or even the specific chimeric proteins as disclosed in Examples 4-7 would have any use in treating a disease state

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beyond mere speculation. The art recognizes the clinical significance of DNA methylation for treatment of diseases involved in aberrant gene expression, e.g., cancer. Singal et al. (*Blood* 93:4059-4070) teach "[s]elective modulation of DNA methylation may therefore have important clinical implications for the prevention and treatment of cancer" (page 4067). However, the art also recognizes the unpredictability that exists as the technology remains immature. Singal et al. teach "[t]o develop safe and effective strategies for therapeutic alteration of DNA methylation, the factors that regulate the specificity of both the methylation and demethylation processes must be more fully understood" and that "understanding the factors involved in DNA methylation-induced gene silencing will facilitate attempts to selectively affect gene expression" (page 4067). Furthermore, even if the specification had provided sufficient guidance as to a disease treatable by administering a "pharmaceutical composition" comprising said vector, the specification provides no guidance as to what, besides said vector, would compose such a composition. Making and testing the infinite number of compositions to find one that is effective would constitute undue experimentation. Therefore, the specification fails to enable one of ordinary skill in the art how to make and/or use the "pharmaceutical composition" encompassed by the claims.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of chimeric proteins and methods of use thereof, encoding nucleic acids, host cells, and pharmaceutical compositions as described above. Based on the quantity of experimentation necessary, lack of guidance and working examples, the unpredictability of the art, and the breadth of the claims, undue experimentation would be required for a skilled artisan to make and/or use the claimed invention. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

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6. Claim 9 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ a novel vector. Since the vector is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The claimed vector sequence is not fully disclosed, nor has the sequence required for its construction been shown to be publicly known and freely available. The enablement requirements of 35 U.S.C. § 112, first paragraph may be satisfied by a deposit of the vector. The specification does not disclose a repeatable process to obtain the vector and it is not apparent if the vector is readily available to the public. Accordingly, it is deemed that a deposit of the vector should have been made in accordance with 37 CFR 1.801-1.809.


Conclusion

7. All claims are rejected. No claim is in condition for allowance.

8. Claims 1-14, 18, 24-26, 29, and 42-46 would appear to be allowable if rewritten to overcome the objection(s) and/or rejection(s) under 35 U.S.C. 112, first and second paragraphs, set forth in this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652


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